

National Aeronautics and  
Space Administration

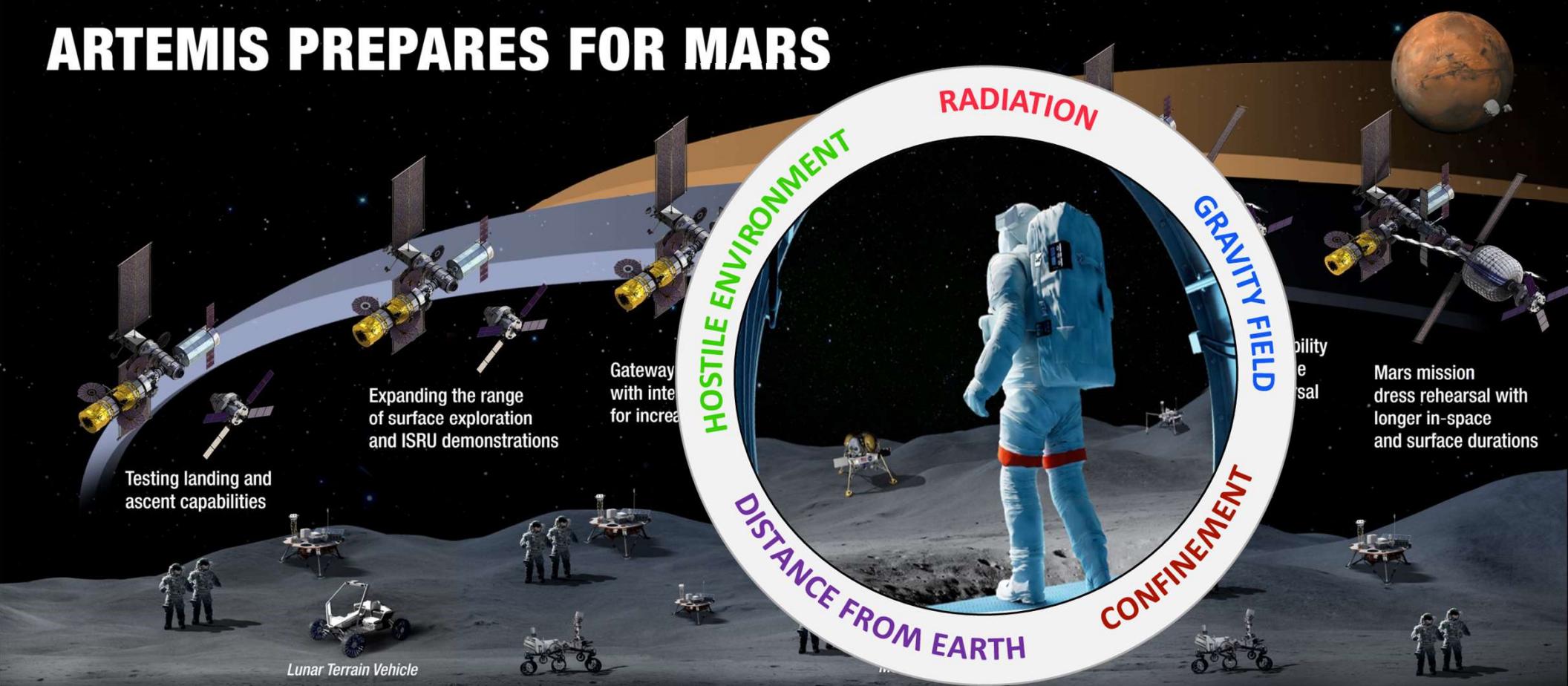


# Genomic and Phenotypic Associations to Predict Human Sensitivity to Space Radiation

## Biological and Physical Sciences

Sylvain Costes  
NASA Ames Research Center

# ARTEMIS PREPARES FOR MARS



## SUSTAINABLE LUNAR ORBIT STAGING CAPABILITY AND SURFACE EXPLORATION

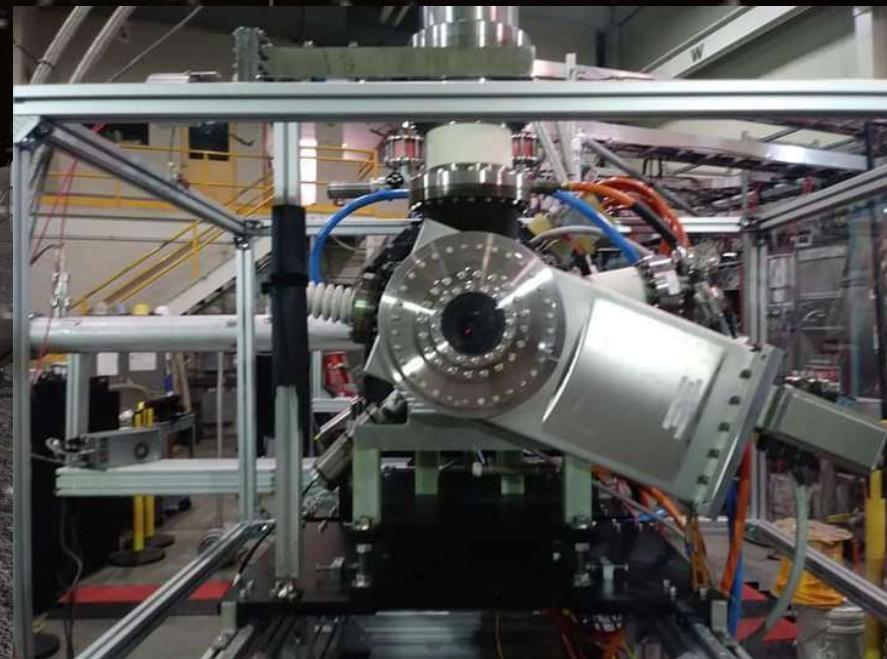
MULTIPLE SCIENCE AND CARGO PAYLOADS | INTERNATIONAL PARTNERSHIP OPPORTUNITIES | TECHNOLOGY AND OPERATIONS DEMONSTRATIONS FOR MARS

**Galactic Cosmic Rays:**

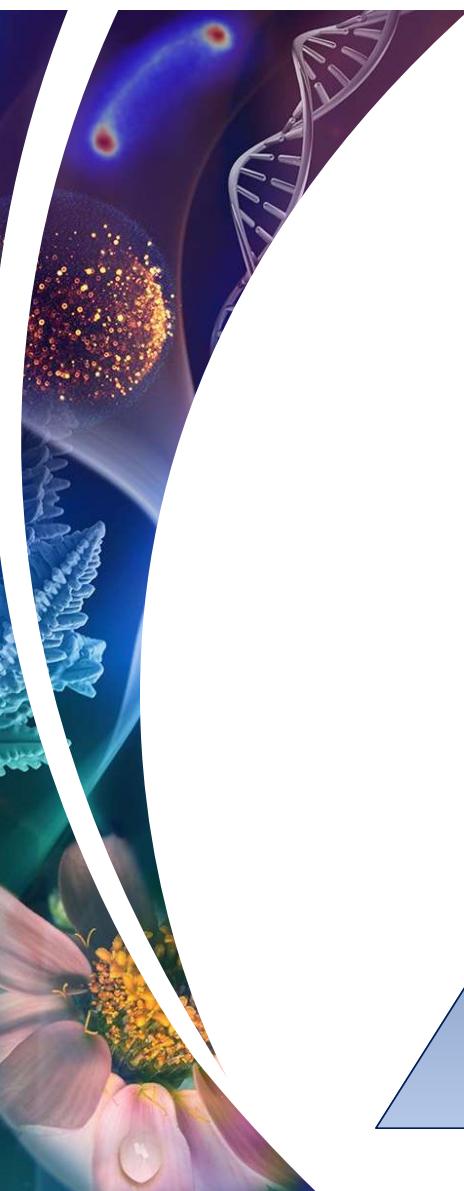
~87% protons

~12%  ${}^4\text{He}$

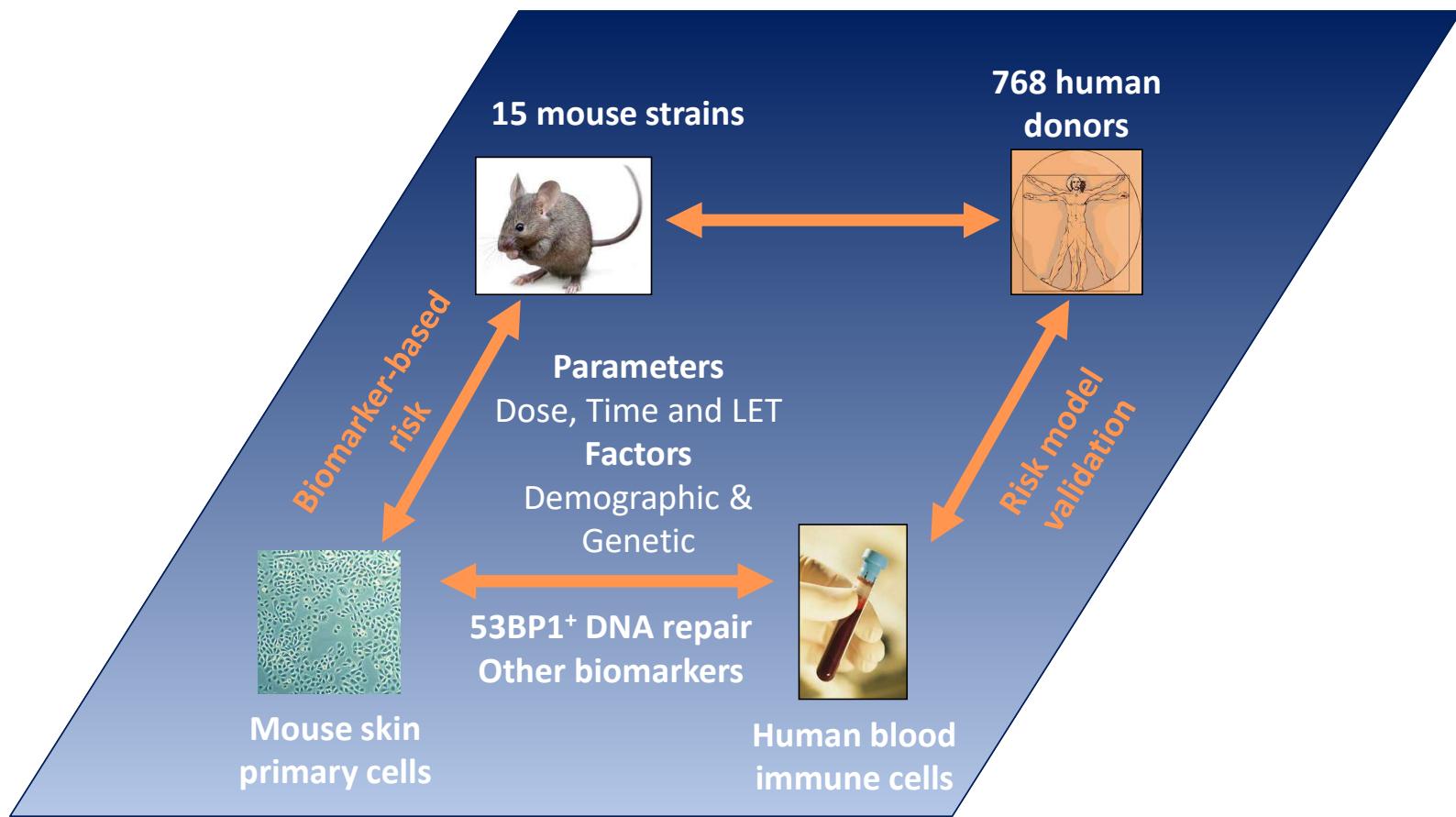
~1% high mass-charge particles through  ${}^{56}\text{Fe}$



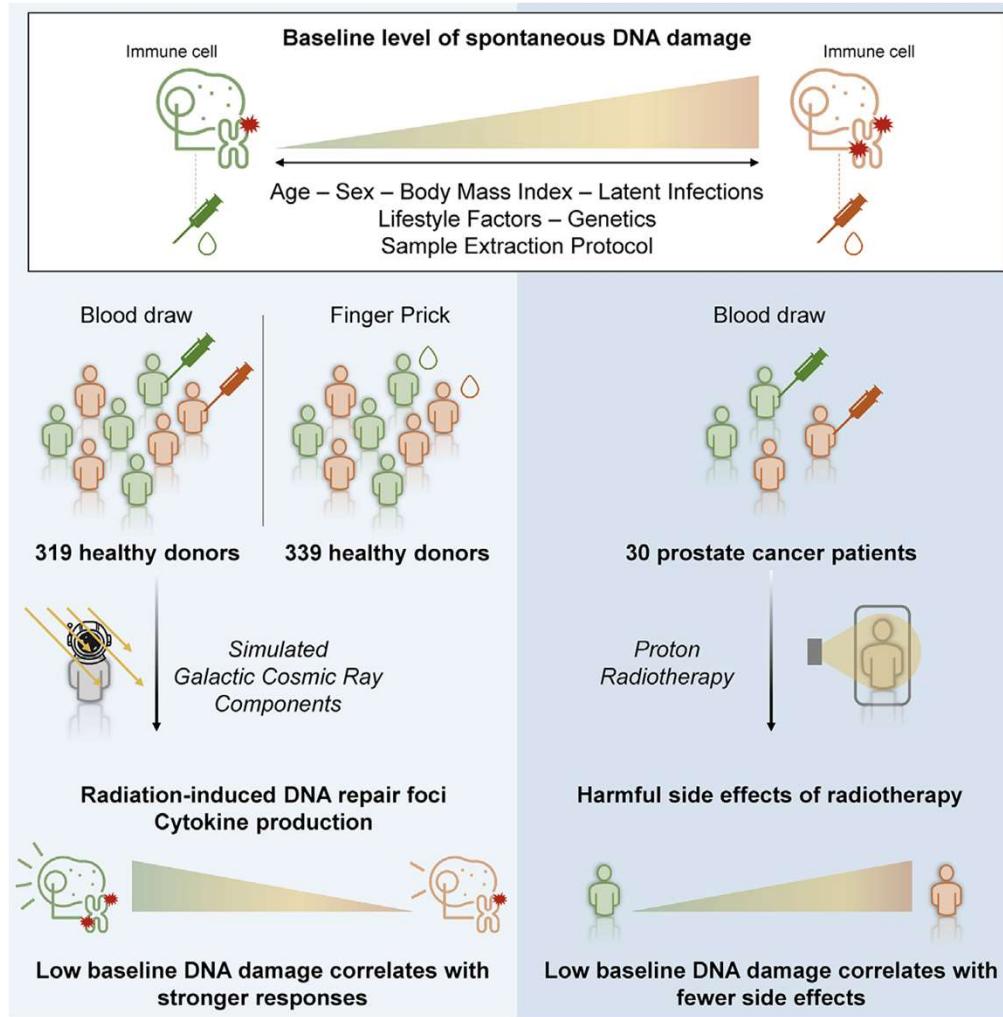
**Simulated at NASA Space Radiation Laboratory in Brookhaven National Lab**



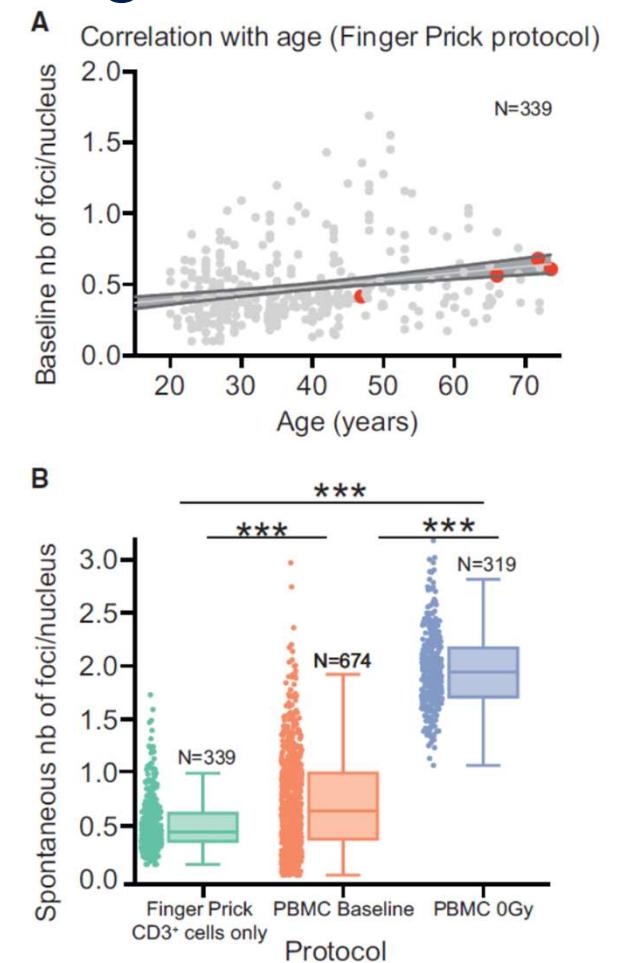
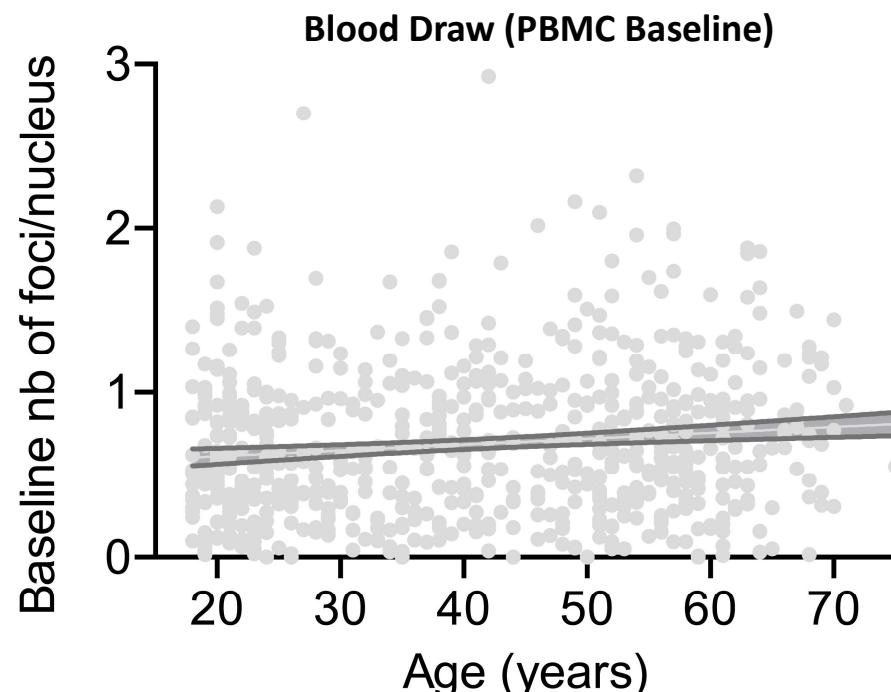
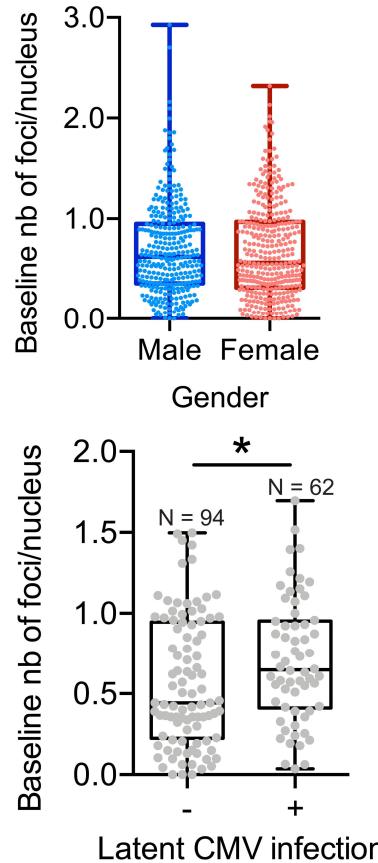
# Blood-based multi-scale model for cancer risk from GCR in genetically diverse populations



# Baseline DNA damage predicts radiosensitivity

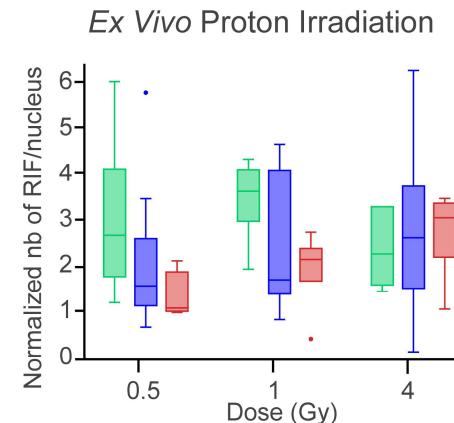
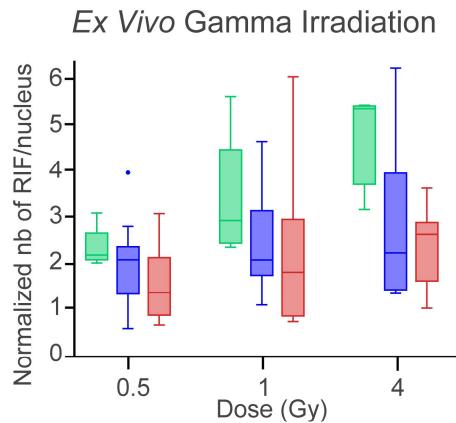


# Baseline DNA damage increases with age and CMV infection



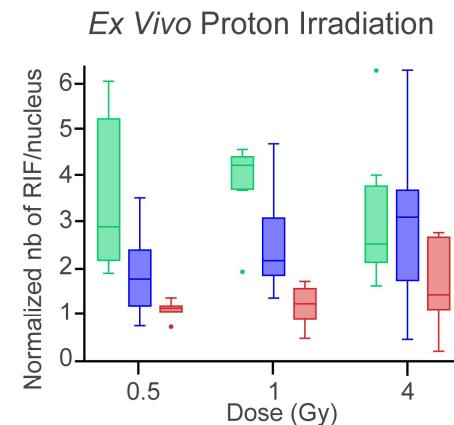
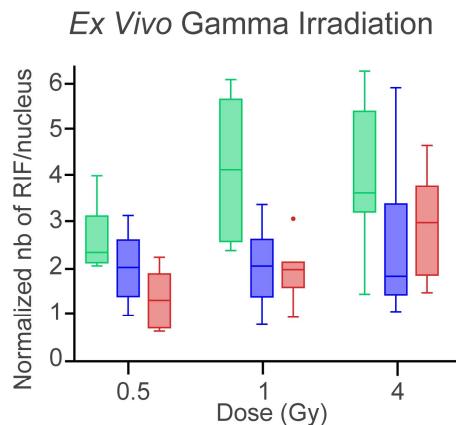


# Baseline DNA damage predicts radiosensitivity in patients *ex vivo*



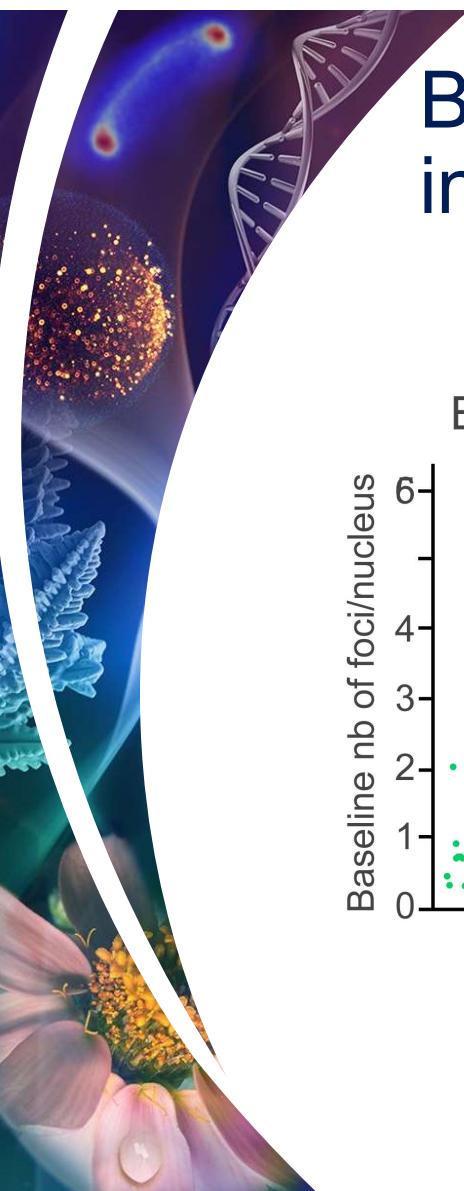
Classification based on clinical response.

- Non Reactive (Green)
- Normally Reactive (Blue)
- Overly Reactive (Red)

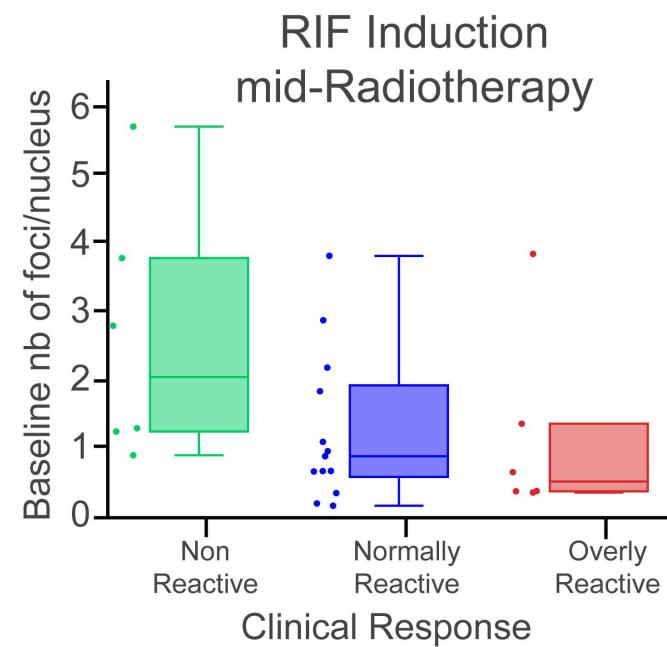
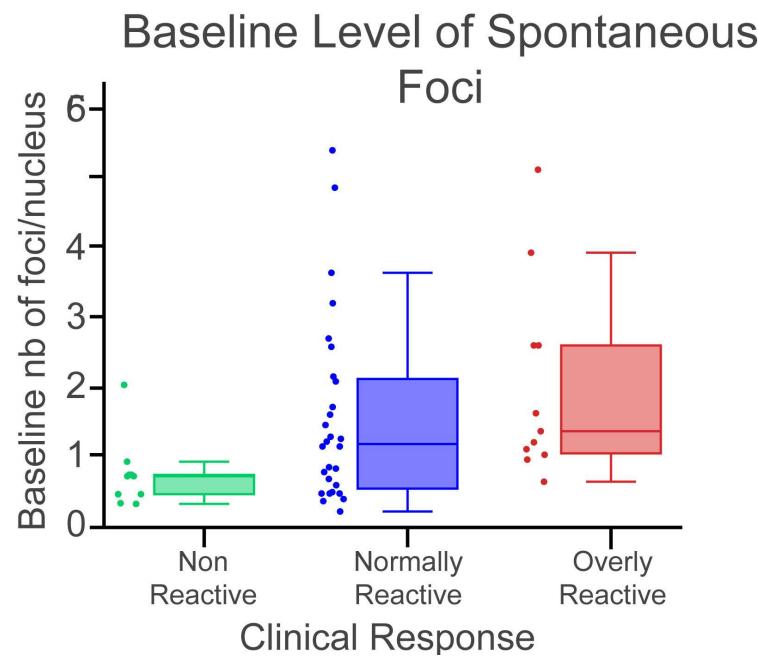


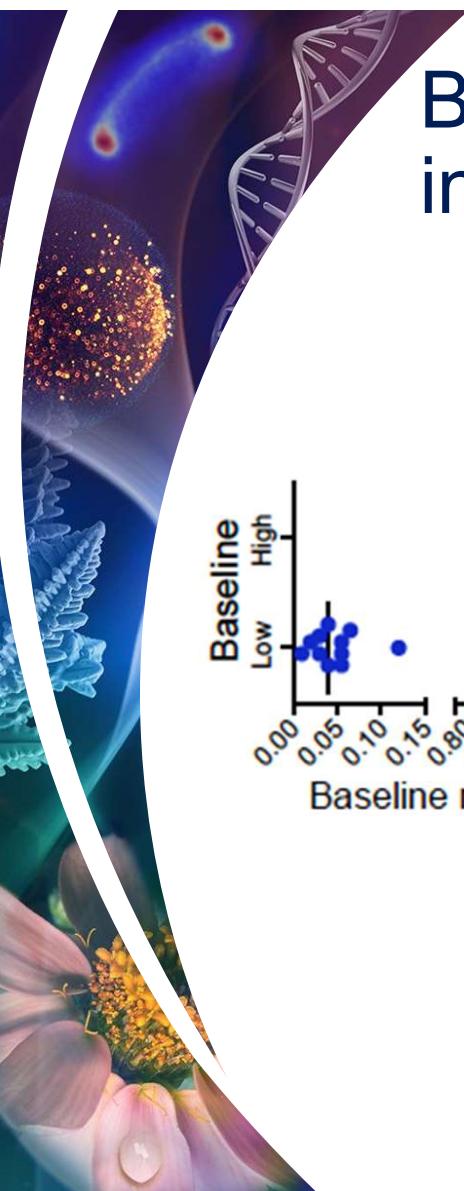
Classification based on baseline DNA damage.

- Low Baseline (Green)
- Medium Baseline (Blue)
- High Baseline (Red)

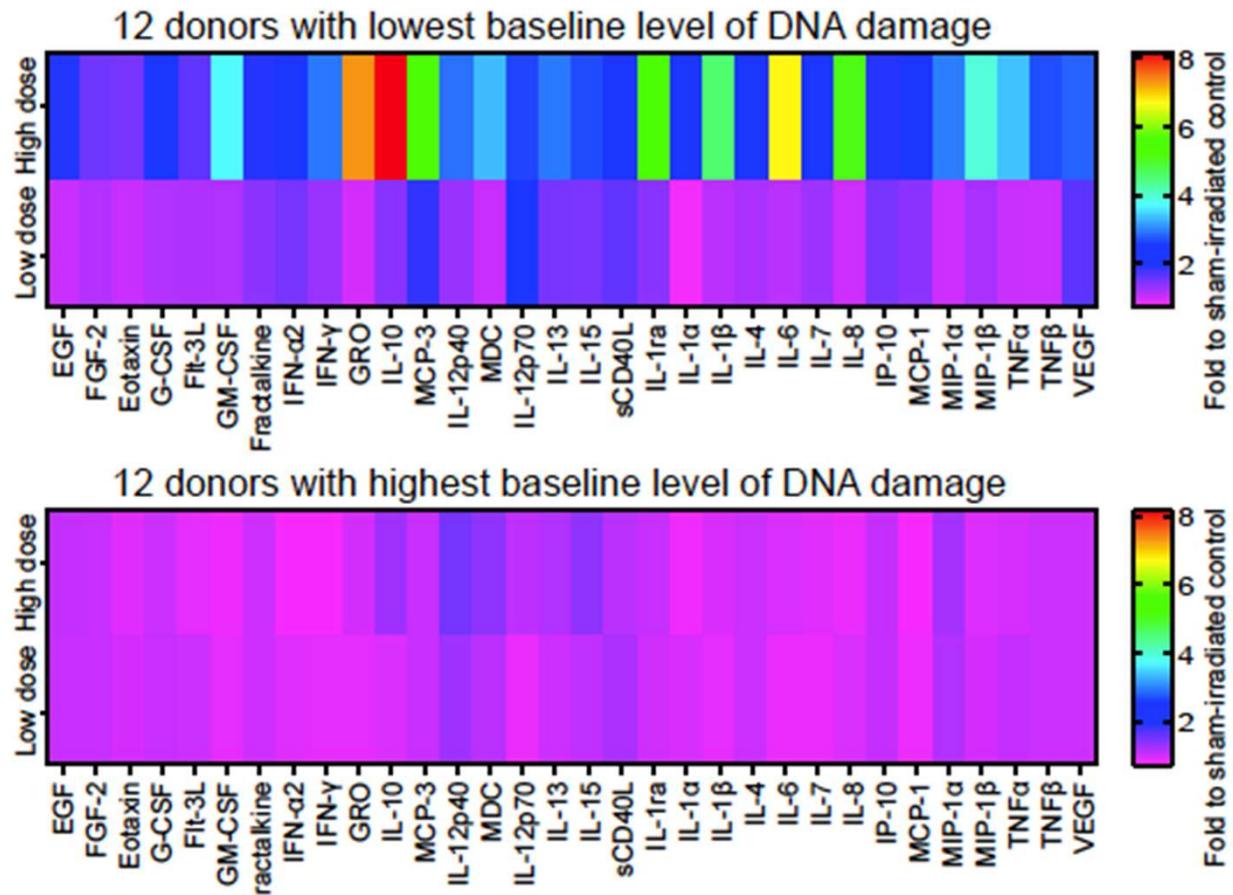
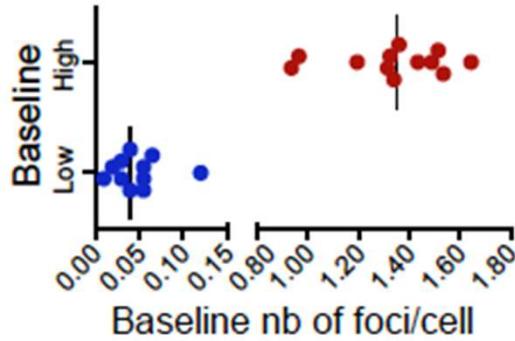


# Baseline DNA damage predicts radiosensitivity in patients *in vivo*

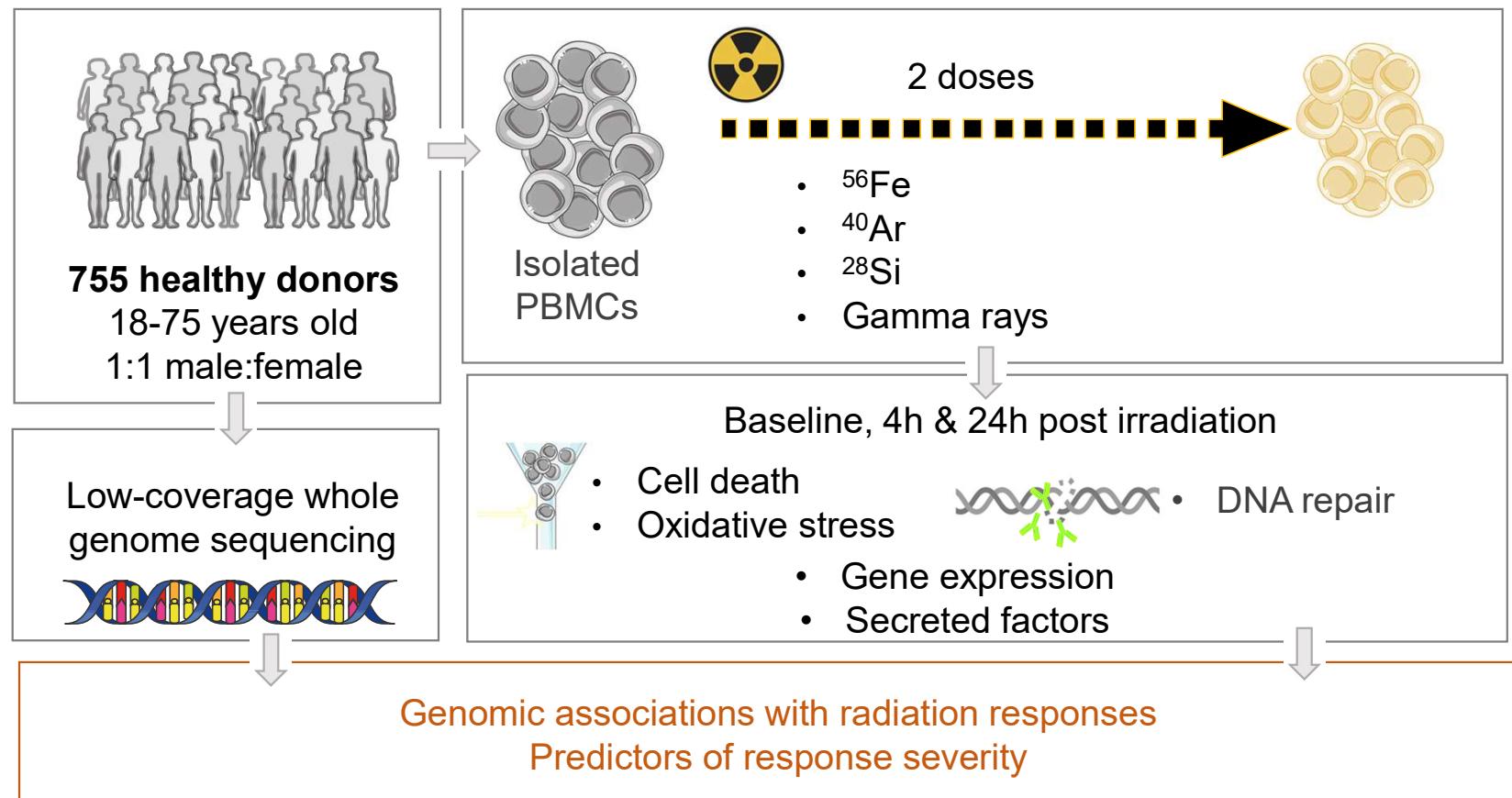




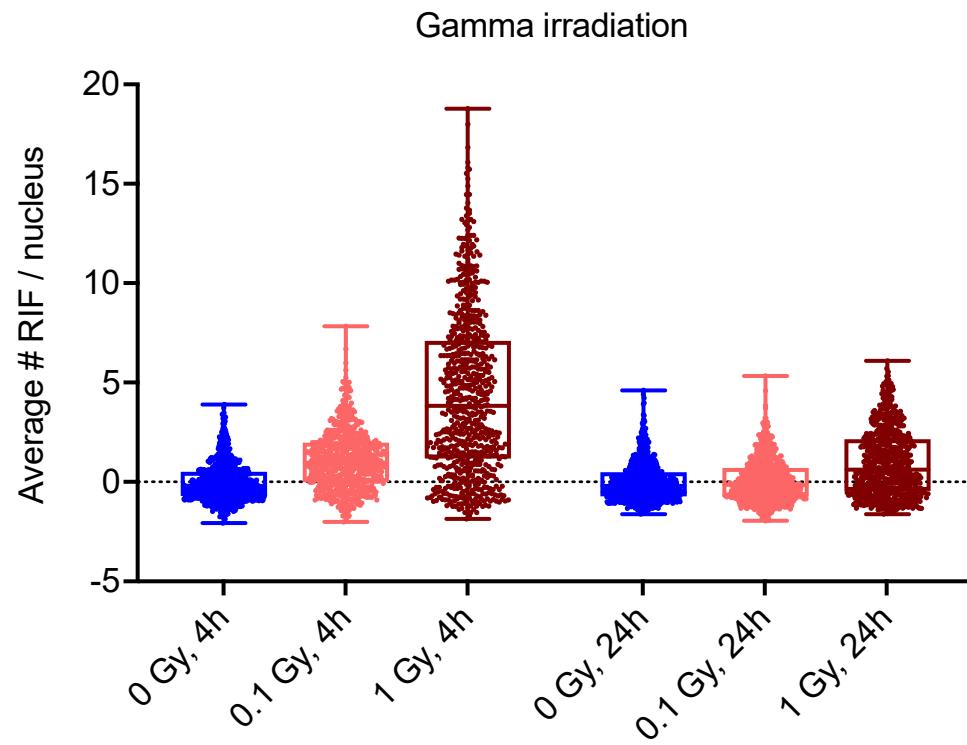
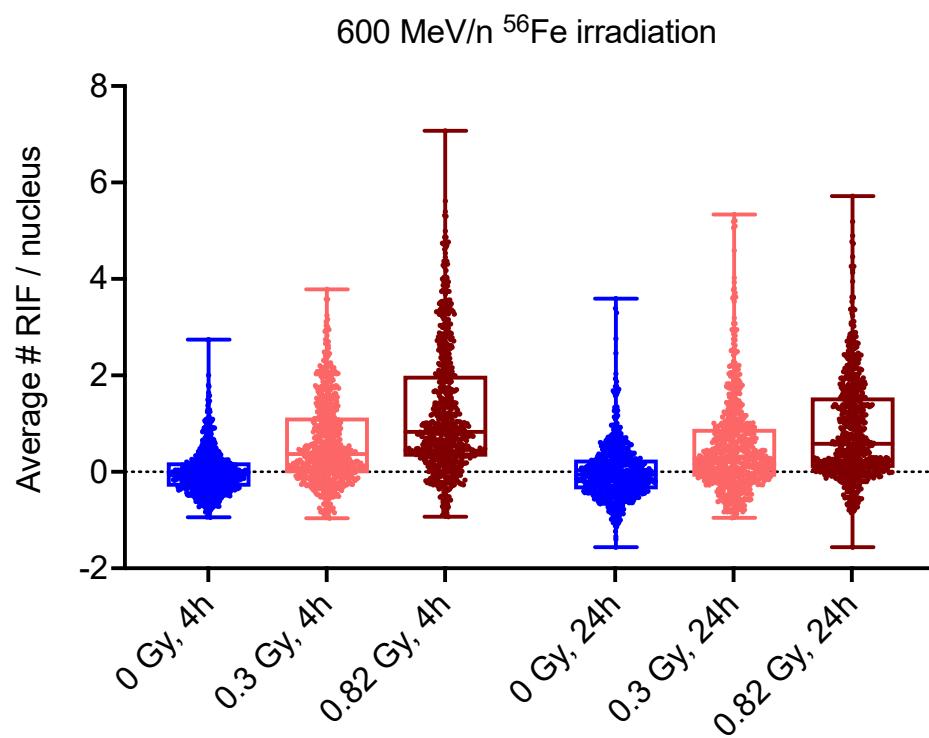
# Baseline DNA damage predicts radiosensitivity in healthy donors *ex vivo*



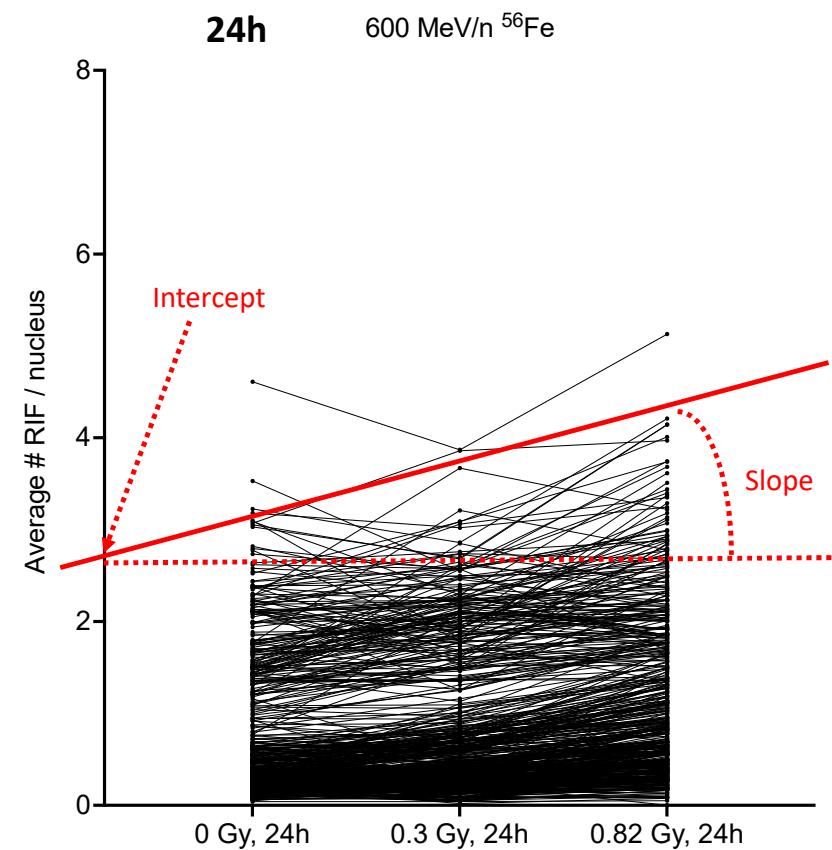
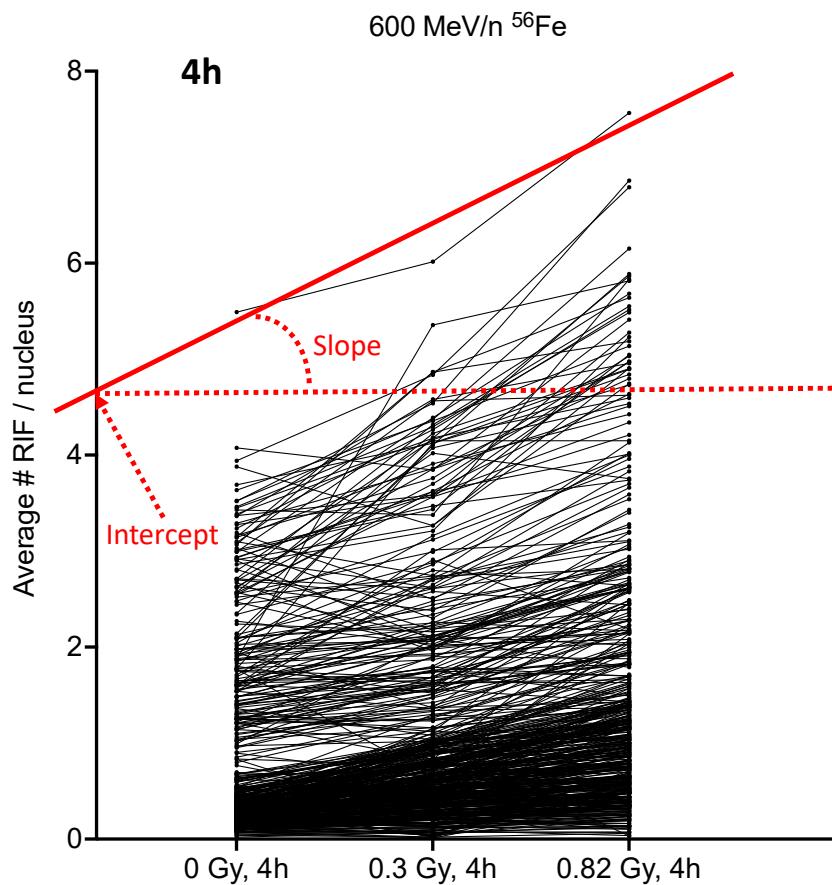
# Experimental setup



# Radiation-induced DNA damage



# Defining radiosensitivity: slopes to describe the *rate* of radiation-induced DNA damage

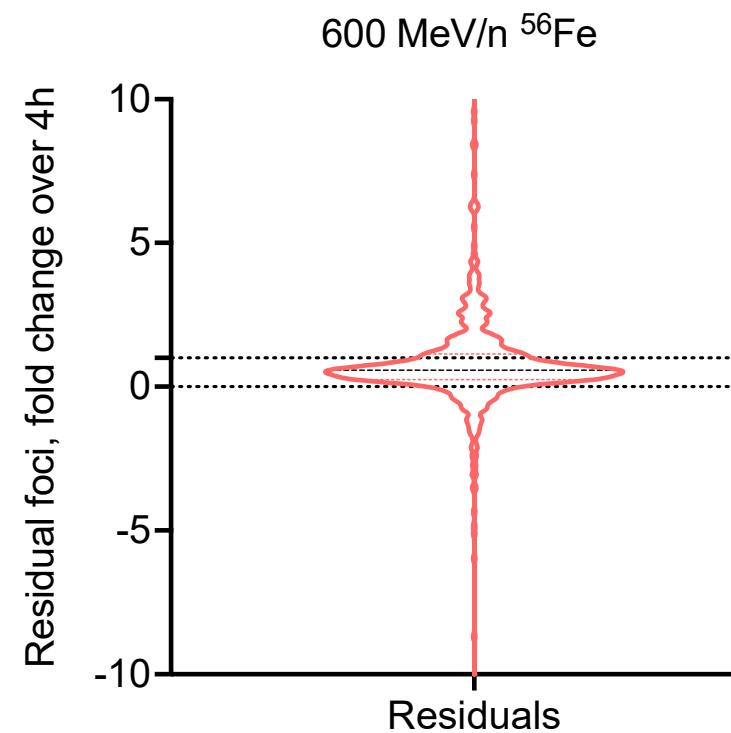


# Defining radiosensitivity: residual foci at 24h to describe *persistent* radiation-induced DNA damage

$$(\text{IR, 24h} - \text{Sham, 24h}) / (\text{IR, 4h} - \text{Sham, 4h})$$

*IR: high dose of irradiation (0.82 Gy for Fe)*

*Sham: 0 Gy irradiation control*



# Radiosensitivity score to describe the response pattern

## FPG = Foci Per Gray

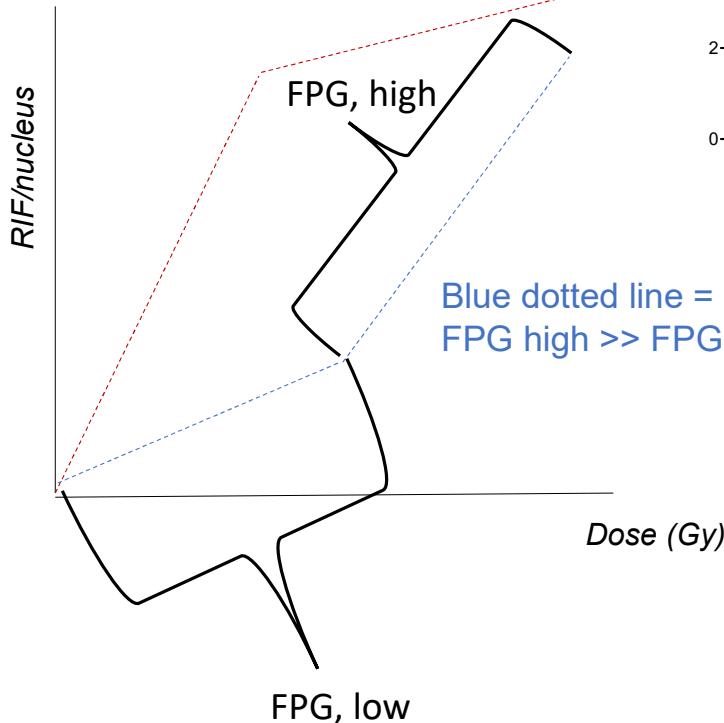
- FPG high =  $(\text{RIF}, 0.82 \text{ Gy} - \text{RIF}, 0.3 \text{ Gy}) / (0.82 - 0.3)$
- FPG low =  $(\text{RIF}, 0.3 \text{ Gy} - \text{RIF}, 0 \text{ Gy}) / 0.3$

## $X,i = \text{FPG high},i - \text{FPG low},i$

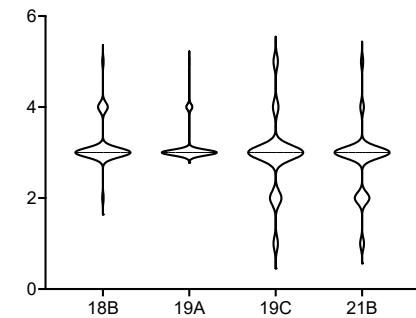
Then, scores based on mean and standard deviation:

- $X < (\text{mean} - 2\text{SD})$ : score **1**
- $(\text{mean} - 2\text{SD}) < X < (\text{mean} - 1\text{SD})$ : score **2**
- $(\text{mean} - 1\text{SD}) < X < (\text{mean} + 1\text{SD})$ : score **3**
- $(\text{mean} + 1\text{SD}) < X < (\text{mean} + 2\text{SD})$ : score **4**
- $X > (\text{mean} + 2\text{SD})$ : score **5**

Red dotted line = “hypersensitive”  
FPG high << FPG low, **score 1**

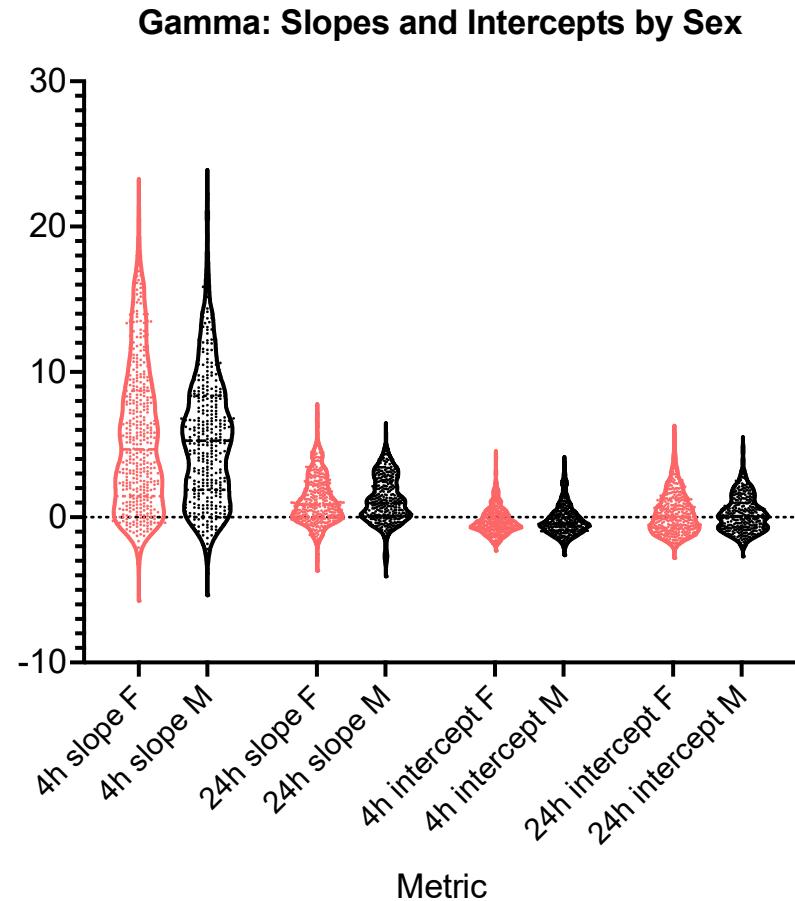
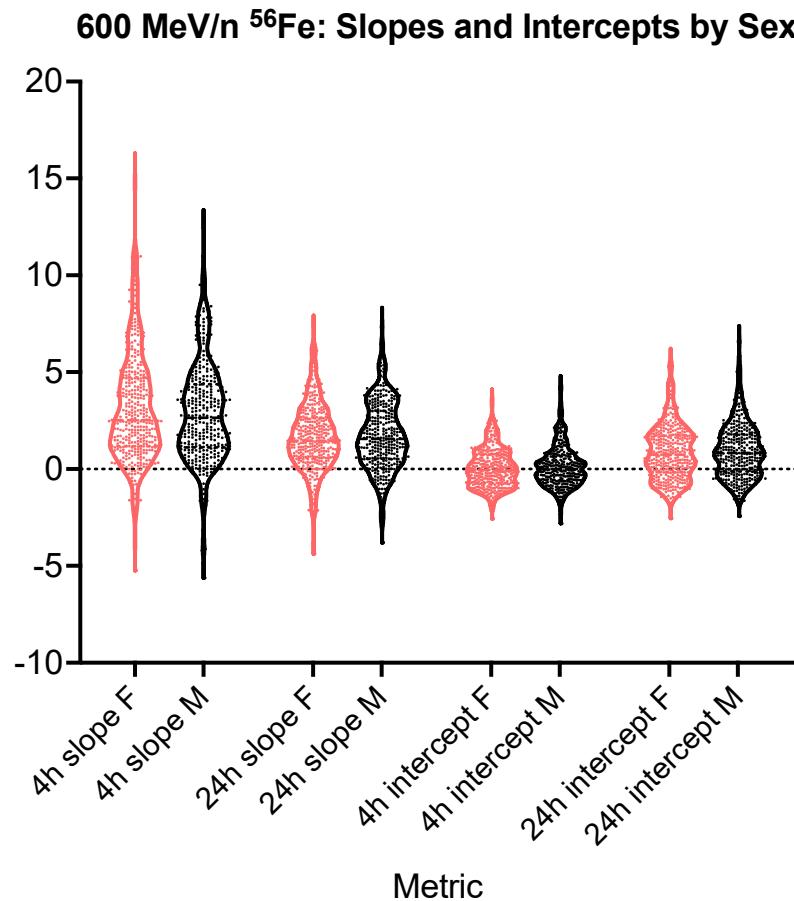


Fe Z score classified per run

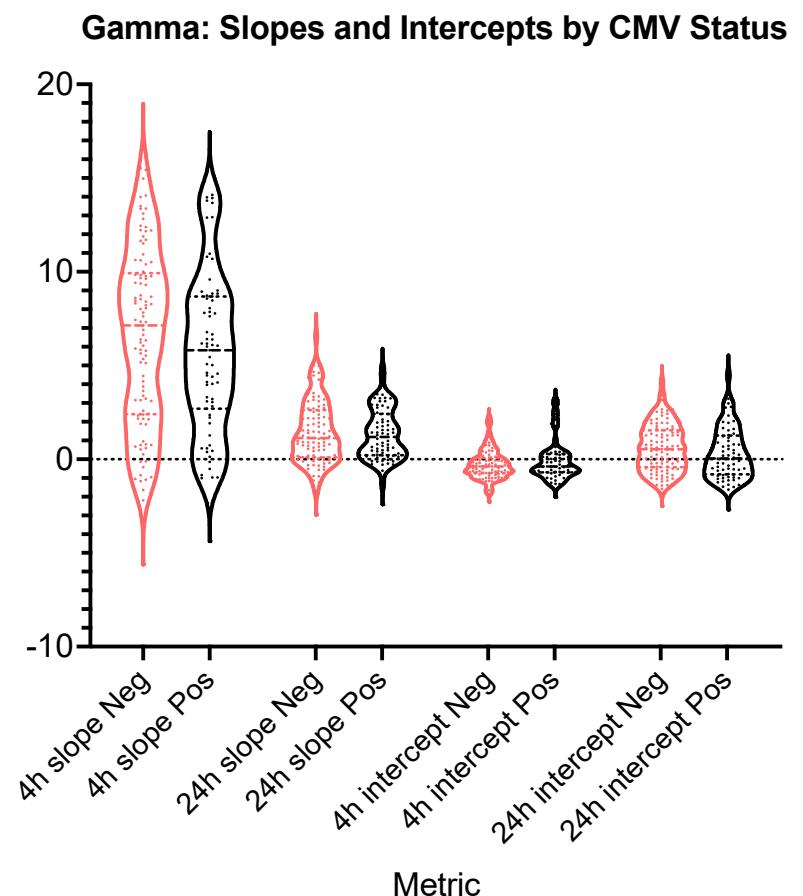
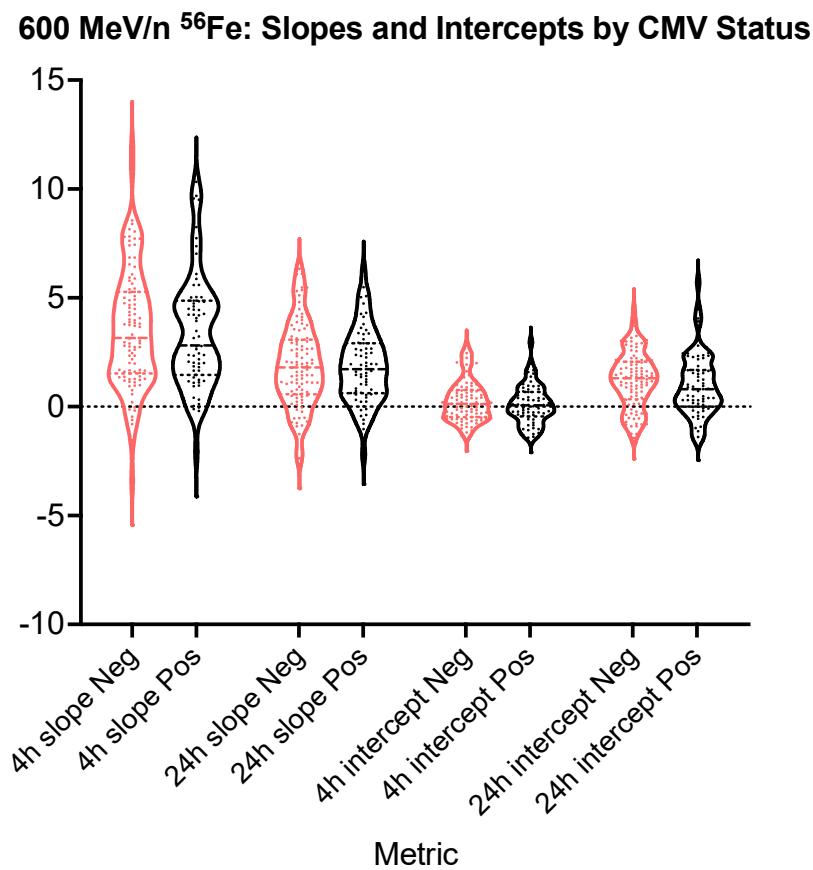


Blue dotted line = “hyposensitive”  
FPG high >> FPG low, **score 5**

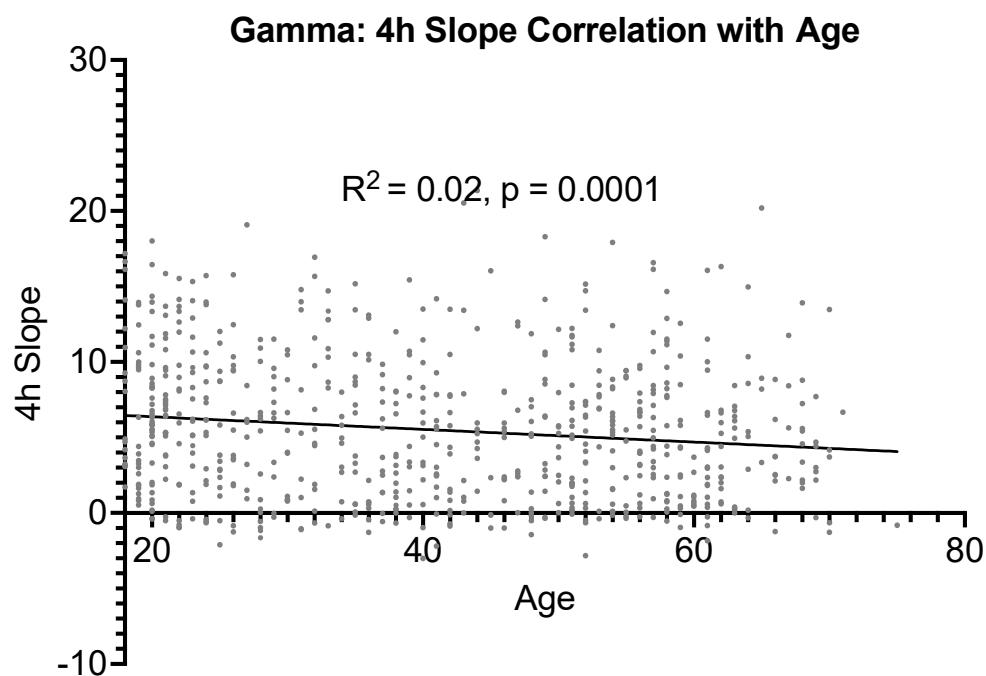
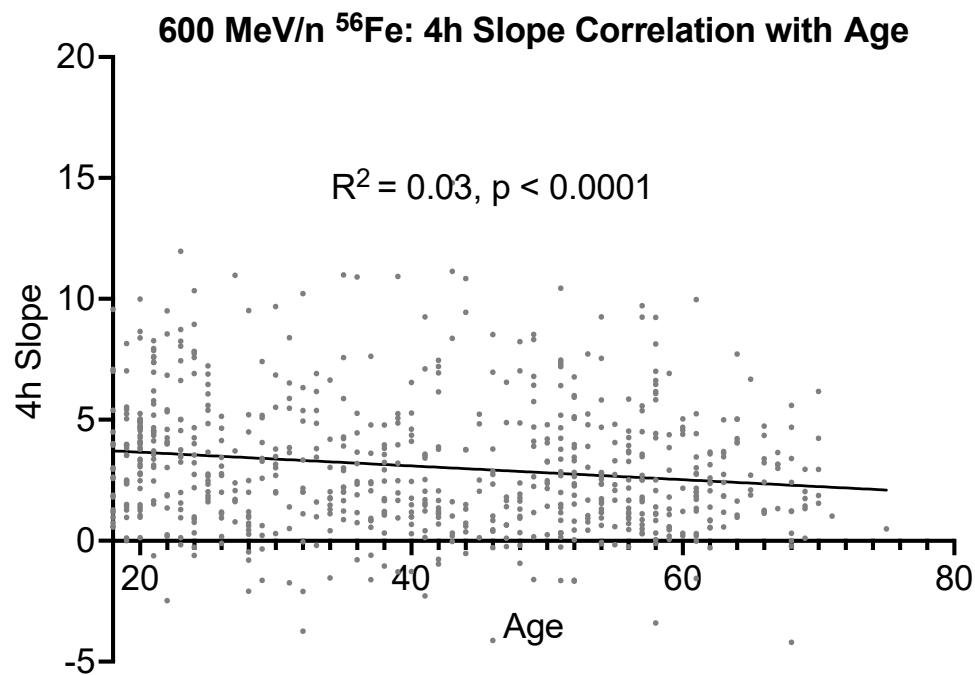
# No sex differences in DNA repair responses



# No differences in DNA repair responses based on CMV status

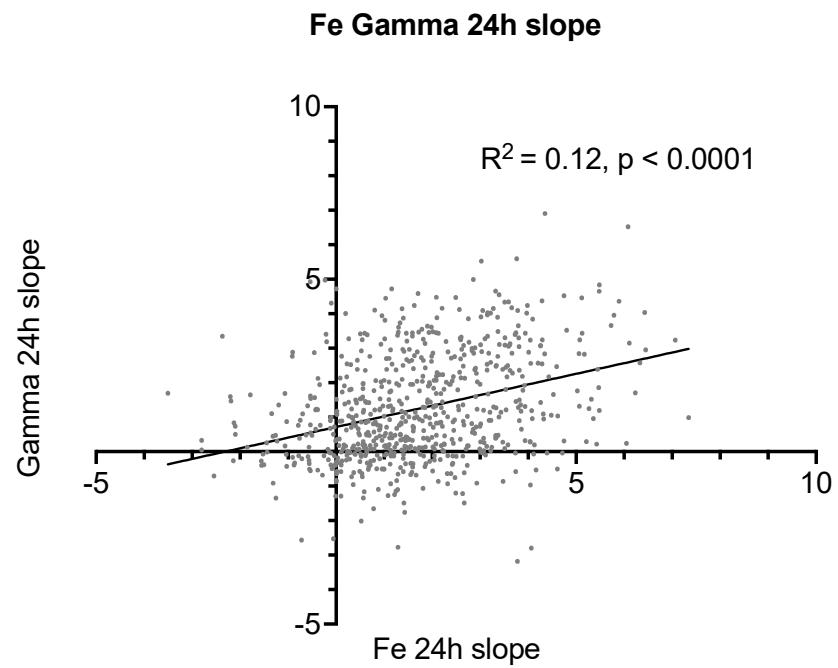
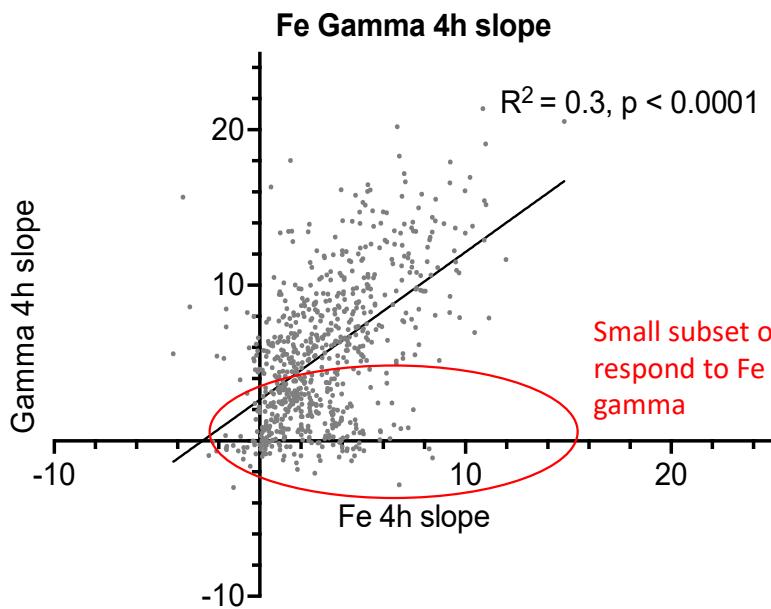


# DNA repair is reduced with age



Slopes are reduced and baselines are increased with age  
“Unhealthy” response: high baseline, low repair after stressor

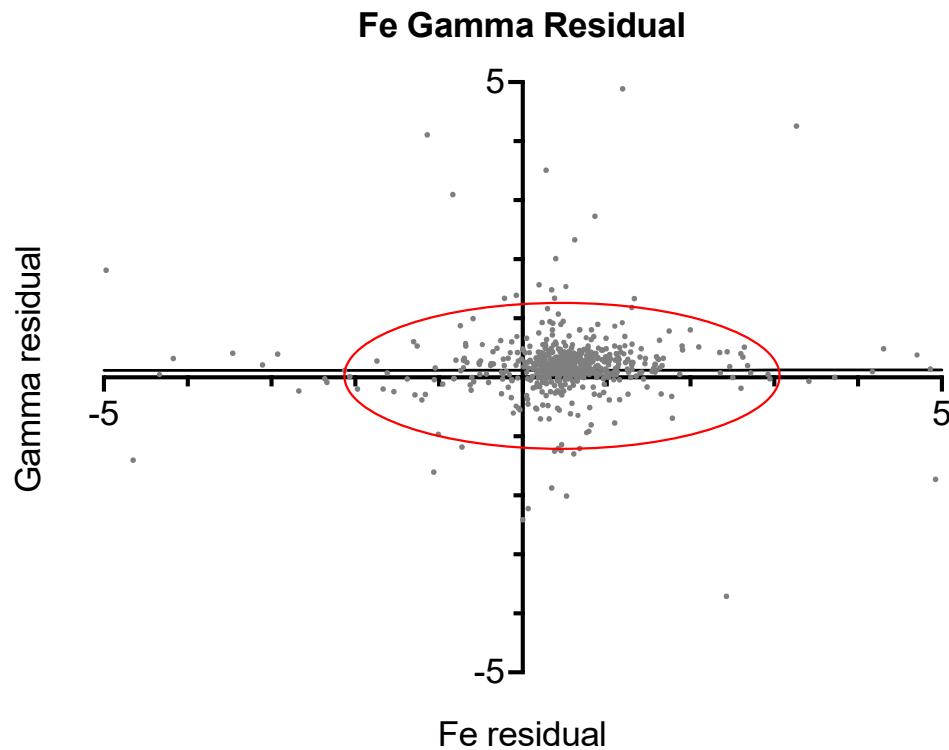
# Comparison between DNA repair responses to 600 MeV/n $^{56}\text{Fe}$ particles and gamma rays



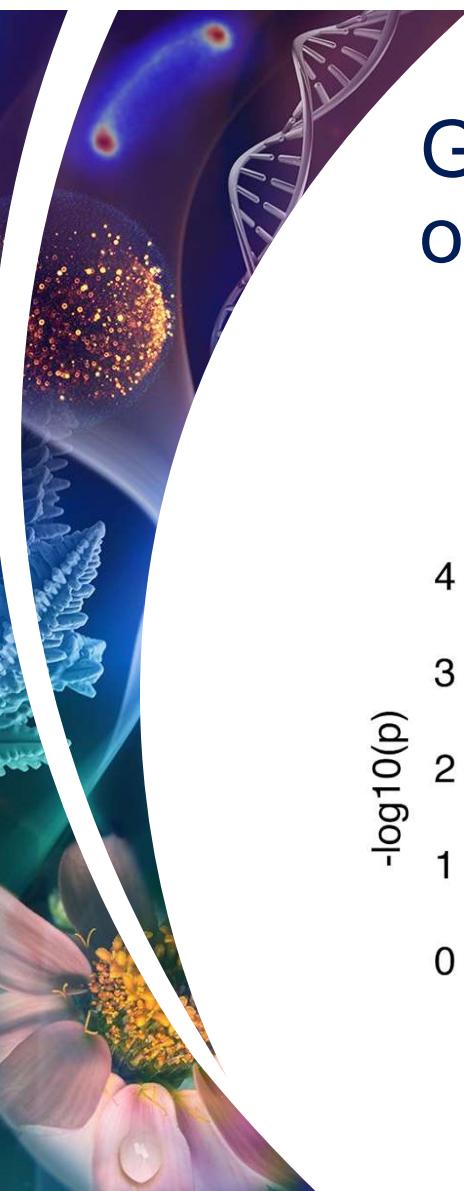
Steeper in gamma than in Fe: Fe leads to clustering of repair sites

Steeper in Fe than in gamma: remaining damage

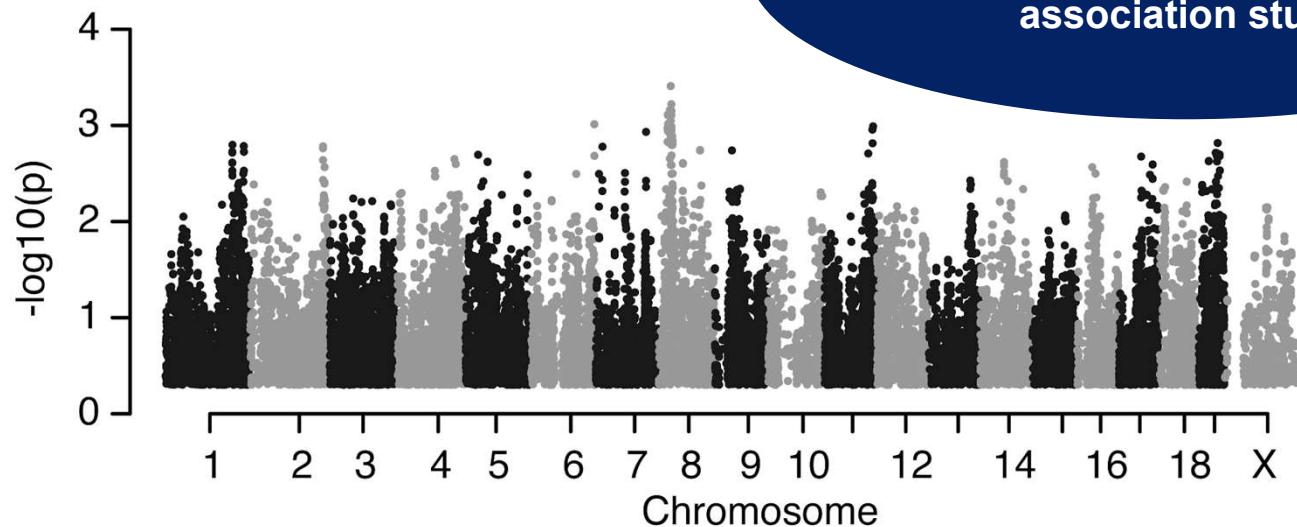
# Comparison of residual DNA damage caused by 600 MeV/n $^{56}\text{Fe}$ particles and gamma rays



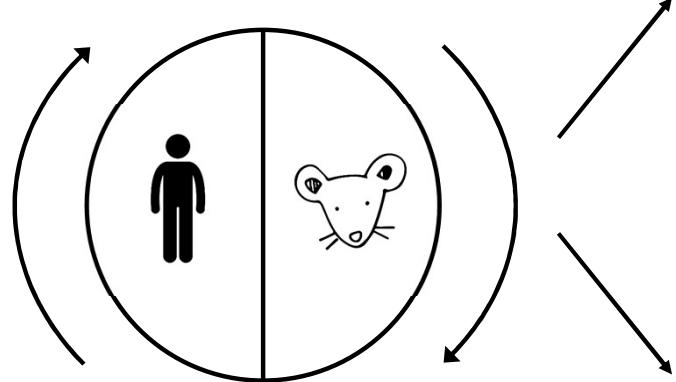
More in Fe than in gamma and not correlated (Fe, not gamma leads to prolonged response)



# Genomic associations with radiosensitivity: ongoing!



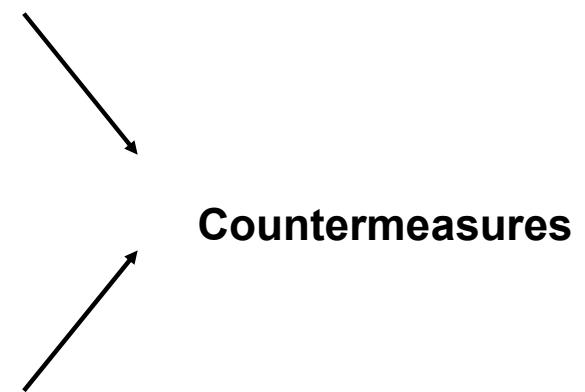
**Characteristics:**  
*Genotype*  
*Baseline responses*  
*Demographics*



**Radiosensitivity  
outputs**

**Predictors and  
Biomarkers**

**Pathways and  
Mechanisms**



**Countermeasures**

# Acknowledgments

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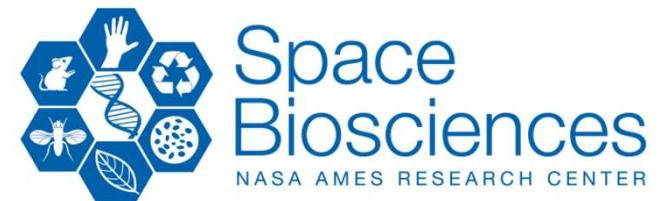
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**Chris Mason**, Cem Meydan, Jonathan Foox

## Brookhaven National Laboratory

Adam Rusek, Peter Guida



## FORMER COLLABORATORS

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